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PATENT & TRADEMARK

METHOD AND APPARATUS FOR CHARACTERIZING MATERIALS BY USING A MECHANICAL RESONATOR

~~FIELD OF THE INVENTION~~

~~The present invention generally relates to methods and apparatus for rapidly screening an array of diverse materials that have been created at known locations on a single substrate surface. More specifically, the invention is directed to the use of ultrasonic and/or mechanical transducers to image and/or evaluate the individual elements of a library of materials. The present invention is also directed to~~ CLAIM OF PRIORITY

[0001] This application is a continuation of 10/266,047, filed on October 7, 2002, which is a continuation of 10/201,181, filed on July 23, 2002, which is a continuation of 09/800,819, filed on March 7, 2001, now U.S. Patent No. 6,494,079, which is a divisional of 09/133,171, filed on August 12, 1998, now U.S. Patent No. 6,393,895, which is a CIP of 08/946,921, filed October 8, 1997, now U.S. Patent No. 6,182,499.

TECHNICAL FIELD

[0002] The present invention is directed to using mechanical oscillators for measuring various properties of fluids (including both liquids and vapors), and more particularly to a method and system using a mechanical oscillator (resonator) for measuring physical, electrical and/or chemical properties of a fluid based on the resonator's response in the fluid to a variable frequency input signal.

BACKGROUND ~~OF THE INVENTION~~ ART

~~The discovery of new materials with novel chemical and physical properties often leads to the development of new and useful technologies. Currently, there is a tremendous amount of activity in the discovery and optimization of materials, such as superconductors, zeolites, magnetic materials, phosphors, catalysts, thermoelectric materials, high and low dielectric materials and the like. Unfortunately, even though the chemistry of extended solids has been extensively explored, few general principles~~

~~have emerged that allow one to predict with certainty the composition, structure and reaction pathways for the synthesis of such solid state compounds.~~

[0003] ~~The preparation of new materials with novel chemical and physical properties is at best happenstance with our current level of understanding. Consequently, the discovery of new materials depends largely on the ability to synthesize and analyze new compounds. Given approximately 100 elements in the periodic table that can be used to make compositions consisting of two or more elements, an incredibly large number of possible new compounds remains largely unexplored. As such, there exists a need in the art for a more efficient, economical and systematic approach for the synthesis of novel materials and for the screening of such materials for useful properties.~~ Companies are turning to combinatorial chemistry techniques for developing new compounds having novel physical and chemical properties. Combinatorial chemistry involves creating a large number of chemical compounds by reacting a known set of starting chemicals in all possible combinations and then analyzing the properties of each compound systematically to locate compounds having specific desired properties. See, for example, U.S. patent application Ser. No. 08/327,513 (published as WO 96/11878), filed Oct. 18, 1994, entitled "The Combinatorial Synthesis of Novel Materials", the disclosure of which is incorporated by reference.

[0004] The virtually endless number of possible compounds that can be created from the Periodic Table of Elements requires a systematic approach to the synthesizing and screening processes. Thus, any system that can analyze each compound's properties quickly and accurately is highly desirable. Further, such a system would be useful in any application requiring quick, accurate measurement of a liquid's properties, such as in-line measurement of additive concentrations in gasoline flowing through a conduit or detection of environmentally-offending molecules, such as hydrogen sulfide, flowing through a smokestack.

~~One of the processes whereby nature produces molecules having novel functions involves the generation of large collections (libraries) of molecules and the systematic screening of those collections for molecules having a desired property. An example of such a process is the humoral immune system which in a matter of weeks sorts through some 10^{12} antibody molecules to find one which specifically binds a foreign pathogen~~

~~(Nisonoffet al., The Antibody Molecule (Academic Press, N.Y., 1975)). This notion of generating and screening large libraries of molecules has recently been applied to the drug discovery process.~~

~~Applying this logic, methods have been developed for the synthesis and screening of large libraries (up to 10^{14} molecules) of peptides, oligonucleotides and other small molecules. Geysen et al., for example, have developed a method wherein peptide syntheses are carried out in parallel on several rods or pins (J. Immun. Meth. 102:259-274 (1987), incorporated herein by reference for all purposes). Generally, the Geysen et al. method involves functionalizing the termini of polymeric rods and sequentially immersing the termini in solutions of individual amino acids. In addition to the Geysen et al. method, techniques have recently been introduced for synthesizing large arrays of different peptides and other polymers on solid surfaces. Pirrung et al have developed a technique for generating arrays of peptides and other molecules using, for example, light-directed, spatially-addressable synthesis techniques (U.S. Pat. No. 5,143,854 and PCT Publication No. WO 90/15070, incorporated herein by reference for all purposes). In addition, Fodor et al. have developed a method of gathering fluorescence intensity data, various photosensitive protecting groups, masking techniques, and automated techniques for performing light-directed, spatially-addressable synthesis techniques (Fodor et al., PCT Publication No. WO 92/10092, the teachings of which are incorporated herein by reference for all purposes).~~

~~Using these various methods, arrays containing thousands or millions of different elements can be formed (U.S. patent application Ser. No. 08/805,727, filed Dec. 6, 1991, the complete disclosure of which is incorporated herein by reference for all purposes). As a result of their relationship to semiconductor fabrication techniques, these methods have come to be referred to as "Very Large Scale Immobilized Polymer Synthesis," or "VLSIPS.TM." technology. Such techniques have met with substantial success in screening various ligands such as peptides and oligonucleotides to determine their relative binding affinity to a receptor such as an antibody.~~

~~The solid phase synthesis techniques currently being used to prepare such libraries involve the sequential coupling of building blocks to form the compounds of interest. For~~

~~example, in the Pirrung et al. method polypeptide arrays are synthesized on a substrate by attaching photoremovable groups to the surface of the substrate, exposing selected regions of the substrate to light to activate those regions, attaching an amino acid monomer with a photoremovable group to the activated region, and repeating the steps of activation and attachment until polypeptides of the desired length and sequence are synthesized. These solid phase synthesis techniques cannot readily be used to prepare many inorganic and organic compounds.~~

~~In PCT WO 96/11878, the complete disclosure of which is incorporated herein by reference, methods and apparatus are disclosed for preparing a substrate with an array of diverse materials deposited in predefined regions. Some of the methods of deposition disclosed in PCT WO 96/11878 include sputtering, ablation, evaporation, and liquid dispensing systems. Using the disclosed methodology, many classes of materials can be generated combinatorially including inorganics, intermetallics, metal alloys, and ceramics.~~

~~In general, combinatorial chemistry refers to the approach of creating vast numbers of compounds by reacting a set of starting chemicals in all possible combinations. Since its introduction into the pharmaceutical industry in the late 80's, it has dramatically sped up the drug discovery process and is now becoming a standard practice in the industry (Chem. Eng. News Feb. 12, 1996). More recently, combinatorial techniques have been successfully applied to the synthesis of inorganic materials (G. Briceno et al., SCIENCE 270, 273-275, 1995 and X.D. Xiang et al., SCIENCE 268, 1738-1740, 1995). By use of various surface deposition techniques, masking strategies, and processing conditions, it is now possible to generate hundreds to thousands of materials of distinct compositions per square inch. These materials include high T_c superconductors, magnetoresistors, and phosphors. Discovery of heterogeneous catalysts will no doubt be accelerated by the introduction of such combinatorial approaches.~~

~~A major difficulty with these processes is the lack of fast and reliable testing methods for rapid screening and optimization of the materials. Recently, a parallel screening method based on reaction heat formation has been reported (F. C. Moates et al., Ind. Eng. Chem. Res. 35, 4801-4803, 1996). For oxidation of hydrogen over a metallic surface, it~~

~~is possible to obtain IR radiation images of an array of catalysts. The hot spots in the image correspond to active catalysts and can be resolved by an infrared camera.~~

~~Screening large arrays of materials in combinatorial libraries creates a number of challenges for existing analytical techniques. For example, traditionally, a heterogeneous catalyst is characterized by the use of a micro-reactor that contains a few grams of porous-supported catalysts. Unfortunately, the traditional method cannot be used to screen a catalyst library generated with combinatorial methods. First, a heterogeneous catalyst library synthesized by a combinatorial chemistry method may contain from a few hundred to many thousands of catalysts. It is impractical to synthesize a few grams of each catalyst in a combinatorial format. Second, the response time of micro-reactors is typically on the order of a few minutes. The time it takes to reach equilibrium conditions is even longer. It is difficult to achieve high-throughput screening with such long response times.~~

~~Another challenge with screening catalyst arrays is the low concentration of components that may be present in the reactions. For example, oxidation of ethylene to ethylene oxide can be carried out over a silver-based catalyst (S. Rebsdat et al., U.S. Pat. Nos. 4,471,071 and 4,808,738). For a surface-supported catalyst with an area of 1 mm by 1 mm and the same activity as the industrial catalyst, only about 10 parts per billion (ppb) of ethylene are converted into the desired ethylene oxide when the contact time is one second.~~

~~Detection of such low component levels in the presence of several atmospheres of reaction mixture is a challenge to analytical methods. Many analytical techniques, including optical methods such as four-wave mixing spectroscopy and cavity ring-down absorption spectroscopy as well as conventional methods such as GC/MS, are excluded because of poor sensitivities, non-universal detectability, and/or slow response. Therefore an apparatus and methodology for screening a substrate having an array of materials that differ slightly in chemical composition, concentration, stoichiometry, and/or thickness is desirable.~~

[0005] It is therefore an object of the invention to measure simultaneously both the physical and the electrical properties of a fluid composition using a mechanical resonator device.

[0006] It is also an object of the invention to detect differences clearly between two or more compounds in a fluid composition by using a mechanical resonator device to measure a composition's physical and electrical properties.

[0007] It is a further object of the invention to use a mechanical resonator device to monitor and measure a physical or chemical transformation of a fluid composition.

[0008] It is also an object of the invention to use a mechanical resonator device to detect the presence of a specific material in a fluid.

SUMMARY OF THE INVENTION

~~The present invention provides methods and apparatus for interrogating an array of diverse materials located at predefined regions on a single substrate. Typically, each of the individual materials will be screened or interrogated for one or more properties. Once screened, the individual materials may be ranked or otherwise compared relative to each other with respect to the material characteristics under investigation.~~

~~In one aspect of the invention, systems and methods are provided for imaging a library of materials using ultrasonic imaging techniques. The system includes one or more devices for exciting an element of the library such that acoustic waves are propagated through, and from, the element. The acoustic waves propagated from the element are detected and processed to yield a visual image of the library element. The acoustic wave data can also be processed to obtain information about the elastic properties of the library element. In one embodiment of the invention, the acoustic wave detector scans the library in a raster pattern, thus providing a visual image of the entire library.~~

~~In another aspect of the invention, systems and methods are provided for generating acoustic waves in a tank filled with a coupling liquid. The library of materials is then placed in the tank and the surface of the coupling liquid is scanned with a laser beam. The structure of the liquid surface disturbed by the acoustic wave is recorded, the recorded disturbance being representative of the physical structure of the library. Accordingly, a correspondence between the surface pattern and the geometry and~~

~~mechanical properties of the library can be constructed.~~

~~In another aspect of the invention, a probe that includes a mechanical resonator is used to evaluate various properties (e.g., molecular weight, viscosity, specific weight, elasticity, dielectric constant, conductivity, etc.) of the individual liquid elements of a library of materials. The resonator is designed to ineffectively excite acoustic waves. The frequency response of the resonator is measured for the liquid element under test, preferably as a function of time. By calibrating the resonator to a set of standard liquids with known properties, the properties of the unknown liquid can be determined. An array of library elements can be characterized by a single scanning transducer or by using an array of transducers corresponding to the array of library elements.~~

[0009] The present invention includes a method for measuring a property of a fluid composition using a tuning fork resonator, the method comprising:

placing the tuning fork resonator in the fluid composition such that at least a portion of the tuning fork resonator is submerged in the fluid composition;

applying a variable frequency input signal to a measurement circuit coupled with the tuning fork resonator to oscillate the tuning fork resonator;

varying the frequency of the variable frequency input signal over a predetermined frequency range to obtain a frequency-dependent resonator response of the tuning fork resonator; and

determining the property of the fluid composition based on the resonator response.

[0010] The method can also measure a plurality of fluid compositions, wherein the fluid compositions are liquid compositions, using a plurality of tuning fork resonators, wherein the method further comprises:

providing an array of sample wells;

placing each of said plurality of liquid compositions in a separate sample well;

placing at least one of said plurality of tuning fork resonators in at least one sample well;

applying a variable frequency input signal to a measurement circuit coupled with each tuning fork resonator in said at least one sample wells to oscillate each tuning fork resonator associated with each of said at least one sample well;

varying the frequency of the variable frequency input signal over a predetermined frequency range to obtain a frequency-dependent resonator response of each tuning fork resonator associated with said at least one sample well; and

analyzing the resonator response of each tuning fork resonator associated with said at least one sample well to measure a property of each liquid composition in said at least one sample well.

[0011] Accordingly, the present invention is directed primarily to a method using a mechanical piezoelectric quartz resonator ("mechanical resonator") for measuring physical and electrical properties, such as the viscosity density product, the dielectric constant, and the conductivity of sample liquid compositions in a combinatorial chemistry process. The detailed description below focuses primarily on thickness shear mode ("TSM") resonators and tuning fork resonators, but other types of resonators can be used, such as tridents, cantilevers, torsion bars, bimorphs, or membrane resonators. Both the TSM resonator and the tuning fork resonator can be used to measure a plurality of compounds in a liquid composition, but the tuning fork resonator has desirable properties that make it more versatile than the TSM resonator.

[0012] The mechanical resonator is connected to a measuring circuit that sends a variable frequency input signal, such as a sinusoidal wave, that sweeps over a predetermined frequency range, preferably in the 25-30 kHz range for the tuning fork resonator and in a higher range for the TSM resonator. The resonator response over the frequency range is then monitored to determine selected physical and electrical properties of the liquid being tested. Although both the TSM resonator and the tuning fork resonator can be used to test physical and electrical properties, the tuning fork resonator is an improvement over the TSM resonator because of the tuning fork's unique response characteristics and high sensitivity.

[0013] Both the TSM resonator and the tuning fork resonator can be used in combinatorial chemistry applications according to the present invention. The small size and quick response of the tuning fork resonator in particular makes it especially suitable for use in combinatorial chemistry applications, where the properties of a vast number of chemicals must be analyzed and screened in a short time period. In a preferred embodiment, a plurality of sample wells containing a plurality of liquid compositions are disposed on an array. A plurality of TSM or tuning fork resonators are dipped into the liquid compositions, preferably one resonator per composition, and then oscillated via the measuring circuit. Because the resonating characteristics of both the TSM resonator and the tuning fork resonator virtually eliminate the generation of acoustic waves, the size of the sample wells can be kept small without the concern of acoustic waves reflecting from the walls of the sample wells. In practice, the tuning forks can be oscillated at a lower frequency range than TSM resonators, making the tuning forks more applicable to real-world applications and more suitable for testing a wide variety of compositions, including high molecular weight liquids.

[0014] In another embodiment of the invention, the mechanical resonator is coated with a material to change the resonator's characteristics. The material can be a general coating to protect the resonator from corrosion or other problems affecting the resonator's performance, or it can be a specialized "functionalization" coating that changes the resonator's response if a selected substance is present in the composition being tested by the resonator.

[0015] To obtain a more complete range of characteristics for a selected fluid composition, multiple resonators having different resonator characteristics can be connected together as a single sensor for measuring the fluid composition. The resonator responses from all of the resonators in the sensor can then be correlated to obtain additional information about the composition being tested. By using resonators having different characteristics, the fluid composition can be tested over a wider frequency range than a single resonator. Alternatively, a single resonator that can be operated in multiple mechanical modes (e.g. shear mode, torsion mode, etc.) can be used instead of the multiple resonators. The resonator responses corresponding to each mode would be correlated to obtain the additional information about the composition.

[0016] The mechanical resonator system of the present invention, particularly a system using the tuning fork resonator, can also be used to monitor changes in a particular liquid by keeping the resonator in the liquid composition as it undergoes a physical and/or chemical change, such as a polymerization reaction. The invention is not limited to measuring liquids, however; the quick response of the tuning fork resonator makes it suitable for measuring the composition of fluid compositions, both liquid and vaporous, that are flowing through a conduit to monitor the composition of the fluid.

~~A further understanding of the nature and advantages of the inventions herein may be realized by reference to the remaining portions of the specification and the attached drawings.~~

BRIEF DESCRIPTION OF THE DRAWINGS

[0017] FIGS. 1a and 1b are cross-sectional views of a TSM resonator plate and a tuning fork resonator tine used in preferred embodiments of the present invention, respectively;

[0018] FIG. ~~1 is an illustration of a transducer-lens system for imaging a library of elements;~~2 is a block diagram illustrating an example of a composition testing system of the present invention;

[0019] FIG. ~~2 illustrates an ultrasonic imaging system utilizing a piezoelectric transducer array;~~ 3 is a representative diagram illustrating oscillation characteristics of the tuning fork resonator used in a preferred embodiment of the present invention;

~~FIG. 3 illustrates the oscillation mode of a tuning fork resonator;~~

~~FIG. 4 illustrates the oscillation mode of a bimorph/unimorph resonator;~~

FIGS. ~~5a and 5b are cross-sectional views of a TSM resonator plate and a tuning fork resonator tine used in preferred embodiments of the present invention, respectively;~~

~~FIG. 6 illustrates an embodiment of the invention used to determine the average molecular weight of polystyrene in toluene during polymerization;~~

~~FIG. 7 is a graph of the frequency response of a tuning fork resonator for pure toluene~~4a and ~~four different molecular weights of polystyrene;~~

~~FIG. 8 is a graph of a calibration curve corresponding to the data shown in FIG. 7;~~

[0020] ~~FIGS. 9a and 9b~~ 4b are simplified schematic diagrams illustrating a tuning fork resonator connection with the measurement circuit in a preferred embodiment of the present invention;

FIG. ~~9c~~4c illustrates a sample response of the representative circuit shown in FIG. ~~9b;~~

~~FIG. 10 illustrates an embodiment of the invention used for high throughput screening of catalyst combinatorial libraries; and~~

[0021] ~~FIG. 11 is a simplified circuit diagram for a multiplexed control circuit suitable for use with the embodiment shown in FIG. 10.~~4b;

[0022] FIGS. ~~12a~~5a and ~~12b~~5b are examples of traces comparing the frequency responses of the TSM resonator and the tuning fork resonator of the present invention, respectively;

[0023] FIGS. ~~13a~~6a and ~~13b~~6b are examples of graphs illustrating the relationship between the viscosity density product and the equivalent serial resistance of the TSM resonator and the tuning fork resonator of the present invention, respectively;

[0024] FIGS. ~~14a~~7a and ~~14b~~7b are examples of graphs illustrating the relationship between the dielectric constant and the equivalent parallel capacitance of the TSM resonator and the tuning fork resonator of the present invention, respectively;

[0025] FIGS. ~~15a~~8a and ~~15b~~8b are examples of graphs illustrating the relationship between the molecular weight of a sample composition and the equivalent serial resistance of the TSM resonator and the tuning fork resonator of the present invention, respectively, in a polymerization reaction;

[0026] FIGS. ~~16a~~9a and ~~16b~~ 9b illustrate another embodiment of the invention using a resonator that is treated with a coating for targeting detection of specific chemicals; and

[0027] FIGS. ~~17a, 17b, and 17c~~10a, 10b and 10c illustrate examples of different multiple resonator sensors of yet another embodiment of the present invention.

DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS

~~Glossary~~

~~The following terms are intended to have the following general meanings as used herein.~~

~~Substrate~~

~~A substrate is a material having a rigid or semi-rigid surface. In many embodiments at least one surface of the substrate will be substantially flat. In some embodiments the~~

~~substrate will contain physical separations between synthesis regions for different materials. Suitable physical separations include, for example, dimples, wells, raised regions, and etched trenches. According to other embodiments, small beads or pellets may be provided on the surface, either alone or within substrate surface dimples. The surface area of the substrate is designed to meet the requirements of a particular application. Typically, the surface area of the substrate is in the range of 1 cm^2 to 400 cm^2. However, other sizes may be used with the present invention, for example surface areas as small as 0.001 cm^2 or as large as 10 m^2 are possible.~~

~~Predefined Region~~

~~A predefined region is a localized area on a substrate that is, was, or is intended to be used for the formation of a specific material. The predefined region may be referred to, in the alternative, as a "known" region, a "reaction" region, a "selected" region, or simply a "region." The predefined region may have any convenient shape, e.g., linear, circular, rectangular, elliptical, or wedge-shaped. Additionally, the predefined region can be a bead or pellet which is coated with the component(s) of interest. In this embodiment, the bead or pellet can be identified with a tag, such as an etched binary bar code, that can be used to identify which components were deposited on the bead or pellet. The area of the predefined regions depends on the application and is typically smaller than about 25 cm^2. However, the predefined regions may be smaller than 10 cm^2, smaller than 5 cm^2, smaller than 1 cm^2, smaller than 1 mm^2, smaller than 0.5 mm^2, smaller than 10,000 μm^2, smaller than 1,000 μm^2, smaller than 100 μm^2, or even smaller than 10 μm^2.~~

~~Radiation~~

~~Radiation refers to energy with a wavelength between 10^{14} and 10^4. Examples of such radiation include electron beam radiation, gamma radiation, x-ray radiation, ultraviolet radiation, visible light, infrared radiation, microwave radiation, and radio waves. Irradiation refers to the application of radiation to a surface or an object.~~

~~Component~~

~~Component is used herein to refer to each of the individual substances that are deposited onto a substrate. Components can act upon one another to produce a~~

~~particular material. Components can react directly with each other or with an external energy source such as radiation, an electric field, or a magnetic field. A third material or a chemical substance can also act upon components. A component can be an element, a chemical, a material, or a mixture of elements and chemicals. Components can form layers, blends or mixtures, or combinations thereof~~

~~Source Material~~

~~The term source material is used herein to refer to the original material from which a component was derived. Source materials can be composed of elements, compounds, chemicals, molecules, etc. that are dissolved in a solvent, vaporized, evaporated, boiled, sublimed, ablated, etc., thus allowing the source materials to deposit onto a substrate during the synthesis process.~~

~~Resulting Material~~

~~The term resulting material is used herein to refer to the component or combination of components that have been deposited onto a predefined region of a substrate. The resulting materials may comprise a single component, or a combination of components that have reacted directly with each other or with an external source. Alternatively, the resulting material may comprise a layer, blend or mixture of components on a predefined region of the substrate. The resulting materials are screened for specific properties or characteristics to determine their relative performance.~~

~~Mixture or Blend~~

~~The term mixture or, interchangeably, blend refers to a collection of molecules, ions, electrons, or chemical substances. Each component in the mixture can be independently varied. A mixture can consist of two or more substances intermingled with no constant percentage composition, wherein each component may or may not retain its essential original properties, and where molecular phase mixing may or may not occur. In mixtures, the components making up the mixture may or may not remain distinguishable from each other by virtue of their chemical structure.~~

~~Layer~~

~~The term layer is used herein to refer to a material that separates one material,~~

~~component, substrate or environment from another. A layer is often thin in relation to its area and covers the material beneath it. A layer may or may not be thin or flat, but once it is deposited it generally covers the entire surface such that it separates the component or substrate below the layer from the component or environment above the layer.~~

~~Heterogeneous Catalysts~~

~~Heterogeneous catalysts enable catalytic reactions to occur with the reactants and catalysts residing in different phases. As used herein, heterogeneous catalysts include, but are not limited to, mixed metal oxides, mixed metal nitrides, mixed metal sulfides, mixed metal carbides, mixed metal fluorides, mixed metal silicates, mixed metal aluminates, mixed metal phosphates, nobel metals, zeolites, metal alloys, intermetallic compounds, inorganic mixtures, inorganic compounds, and inorganic salts.~~

~~Homogeneous Catalysts~~

~~Homogeneous catalysts enable catalytic reactions to occur with the reactants and catalysts residing in the same phase. As used herein, homogeneous catalysts include, but are not limited to, catalysts for the polymerization of one or more olefinic or vinyl monomers. The olefinic monomers include, but are not limited to, ethylene or alpha-olefins containing from 3 to 10 carbon atoms, such as propylene, 1-butene, 1-pentane, 1-hexene, and 1-octene. The vinyl monomers include, but are not limited to, vinyl chloride, vinyl acetate, vinyl acrylate, methylmethacrylate, methyl vinyl ether, ethyl vinyl ether and acetonitrile. The catalysts employed to carry out a polymerization of one or more monomers of this type include, but are not limited to, radical catalysts, cationic catalysts, anionic catalysts, and anionic coordination catalysts.~~

~~Generating Arrays of Materials~~

~~Generally, an array of materials is prepared by successively delivering components of the materials to predefined regions on a substrate, and simultaneously reacting the components to form at least two materials or, alternatively, the components are allowed to interact to form at least two materials. In one embodiment, for example, a first component of a first material is delivered to a first predefined location on a substrate,~~

~~and a first component of a second material is delivered to a second predefined region on the same substrate. Simultaneously with or thereafter, a second component of the first material is delivered to the first region on the substrate, and a second component of the second material is delivered to the second region on the substrate. Each component can be delivered in either a uniform or gradient fashion to produce either a single stoichiometry or, alternatively, a large number of stoichiometries within a single predefined region. The process is repeated, with additional components, to form a vast array of components at predefined locations on the substrate. Thereafter, the components are simultaneously reacted to form at least two materials or, alternatively, the components interact to form at least two materials. As described herein, the components can be sequentially or simultaneously delivered to the predefined regions on the substrate using any of a number of different delivery techniques.~~

~~Numerous combinatorial techniques can be used to synthesize the various arrays of diverse materials on the substrate according to the present invention. For example, in one embodiment a first component of a first and second material is delivered to the predefined regions on the substrate. Then a second component of the first and second materials is delivered to the predefined regions on the substrate. This process continues for the other components (e.g., third, fourth, fifth, etc. components) and/or the other materials (e.g., third, fourth, fifth, etc. materials) until the array is complete. In another embodiment, the array is formed as previously described, but the resulting materials are formed immediately as the components contact each other on the substrate. In yet another embodiment, the array is formed as previously described, but after the various components are delivered to the substrate, a processing step is carried out which allows or causes the components to interact. In still another embodiment, two or more components are delivered to the predefined regions on the substrate using fast sequential or parallel delivery techniques such that the components interact with each other before contacting the substrate.~~

~~Essentially, any conceivable substrate can be employed in the invention. The substrate can be organic, inorganic, biological, nonbiological, or a combination thereof. The substrate can exist in a variety of forms utilizing any convenient shape or configuration. The substrate preferably contains an array of depressions or wells in which the~~

~~synthesis of the library takes place. The substrate preferably forms a rigid support on which to carry out the reactions described herein. The substrate may be any of a wide variety of materials including, for example, polymers, plastics, Pyrex, quartz, resins, silicon, silica or silica-based materials, carbon, metals, inorganic glasses, inorganic crystals, and membranes. Upon review of this disclosure, other substrate materials will be readily apparent to those of skill in the art. Surfaces on the solid substrate can be composed of the same materials as the substrate or, alternatively, they can be different (i.e., the substrates can be coated with a different material). Moreover, the substrate surface can contain thereon an adsorbent (for example, cellulose) to which the components of interest are delivered. The most appropriate substrate and substrate-surface materials will depend on the class of materials to be synthesized and the selection in any given case will be readily apparent to those of skill in the art.~~

~~Generally, physical masking systems can be employed in combination with various deposition techniques in order to apply components onto the substrate, preferably in an array of wells, in a combinatorial fashion. Thus arrays of resulting materials are created within predefined locations or wells on the substrate. The arrays of resulting materials will usually differ in composition and stoichiometry. Although the components are typically dispensed in the form of a liquid, one or more components may be dispensed in the form of a gas or a powder. Therefore primarily solution phase deposition techniques are used including, for example, sol/gel methods, discrete liquid dispensing techniques (e.g. pipettes, syringes, ink jets, etc.), spin coating with lithography, microcontact printing, spraying with masks and immersion impregnation. Other techniques may be used, however, such as sputtering, electron-beam and thermal evaporation, laser deposition, ion beam deposition, chemical vapor deposition, and spray-coating. Dispenser systems can be manual or, alternatively, they can be automated using, for example, robotics techniques. A description of systems and methods for generating arrays of materials can be found in commonly assigned, co-pending patent applications "The Combinatorial Synthesis of Novel Materials", Publication No. WO 95/13278, filed Oct. 18, 1995; "Systems and Methods for the Combinatorial Synthesis of Novel Materials," patent application Ser. No. 08/841,423, filed Apr. 22, 1997; and "Discovery of Phosphor Materials Using Combinatorial~~

~~Synthesis Techniques," provisional patent application Ser. No. 60/039,882, filed Mar. 4, 1997; the complete disclosures of which are incorporated herein by reference for all purposes.~~

~~In some embodiments of the present invention, after the components have been deposited onto or within predefined regions on a substrate, they are reacted using a number of different techniques. For example, the components can be reacted using solution based synthesis techniques, photochemical techniques, polymerization techniques, template directed synthesis techniques, epitaxial growth techniques, by the sol-gel process, by thermal, infrared or microwave heating, by calcination, sintering or annealing, by hydrothermal methods, by flux methods, by crystallization through vaporization of solvent, etc. Furthermore, each predefined region on the substrate can be heated simultaneously or sequentially using heat sources such as focused infrared radiation, resistive heating, etc. Reactants can, for example, be dispensed to the library of elements in the form of a gas or a liquid. Other useful techniques that can be used to react the components of interest will be readily apparent to those of skill in the art. Additionally, components can react with each other instantly, upon contacting each other, or in the air before contacting the substrate.~~

~~Once prepared, the array of resulting materials can be screened for useful properties and/or the resulting materials can be ranked, or otherwise compared, using the methods described herein. Either the entire array or, alternatively, a section thereof (e.g., a row of predefined regions) can be screened using parallel or fast sequential screening. The area and/or volume of the predefined regions varies, as does the number and density of regions per substrate, depending upon the specific intended application. Similarly, the number of different materials contained within an array also varies with the intended application. Resulting materials include, but are not limited to, liquids, dissolved organic or inorganic molecules, non-biological organic polymers, polymers partially or fully dissolved in a solvent, covalent network solids, ionic solids and molecular, inorganic materials, intermetallic materials, metal alloys, ceramic materials, organic material, organometallic materials, composite materials (e.g., inorganic composites, organic composites, or combinations thereof), and homogeneous or heterogeneous catalysts.~~

~~Given the chemical complexity of catalytic systems, the lack of predictive models, the number of possible combinations of metals, counter ions, ligands, and supports, and the time consuming process of evaluating the performance of each catalyst formulation utilizing conventional laboratory pilot reactors, it is not surprising that the search for the optimum catalyst is a time consuming and inefficient process. Thus, a combinatorial approach to the discovery and optimization of catalytic systems, which combines the synthesis of catalyst libraries with the screening tools of this invention, is useful for accelerating the pace of research in this field. The catalyst libraries of the present invention can include organic (e.g., catalytic antibodies), organometallic, heterogeneous or solid state inorganic array elements. For purposes of this invention, a catalyst is defined as any material that accelerates the rate of a chemical reaction and which is either not consumed during the reaction or which is consumed at a rate slower (on a molar basis) than the reaction that is being catalyzed. Organometallic catalyst libraries which can be screened for useful catalytic properties include, but are not limited to, those described in co-pending U.S. patent application Ser. No. 08/898,715, filed Jul. 22, 1997, which is hereby incorporated by reference for all purposes.~~

~~Ultrasonic Imaging~~

~~In this aspect of the invention, systems and methods are provided for imaging libraries of materials with ultrasonic imaging techniques. In a first embodiment, an acoustic apparatus and method for imaging of a library of materials is provided. The apparatus includes a device for generating acoustic waves that can propagate into a member or element of interest within a library and a detector for sensing the propagation and reflection of the acoustic waves from the library elements. The source and the detector of acoustic waves may be the same apparatus, typically a piezoelectric crystal. After detecting the acoustic waves propagated from the element, the library and the acoustic wave detector are moved relative to one another, preferably in a raster scanning pattern. The magnitude and phase of the detected acoustic waves and the corresponding scan pattern of the library are recorded so that visual images of the library can be obtained. In addition, by processing the obtained data in accordance with a model of sample-acoustic beam interaction, information about the elastic properties of individual library members can be calculated. From the relative elastic properties of~~

~~elements in the library, relative measures of such properties as molecular weight, branching, and co-monomer content may be inferred.~~

~~In a second embodiment of the invention, acoustic waves are generated in a tank filled with a coupling liquid using a conventional multi-element ultrasound imaging head or one of custom design. The library of elements is placed within the tank such that acoustic waves move from the transducer through the fluid, across the substrate, and into the elements of the library. The reflections from each interface and from within the individual library elements are recorded by the ultrasound transducer head. Material properties can be calculated from the recorded temporal pattern. Alternatively, the structure or morphology of the surface of the library elements, or a liquid interface deposited on top of them, may be recorded using a laser probe or other imaging system. Furthermore, since the recorded disturbance is representative of the physical structure of the library, a correspondence between the surface pattern and the geometry and mechanical properties of the library can be constructed. Lastly, the collected data can be used to derive microscopic properties of individual elements of the library, for example, sound velocity and attenuation as a function of element position can be derived.~~

~~In a third embodiment of the invention, an acoustic lens excites acoustic waves within elements of the material array. The excited acoustic waves are in a form of short pulses. The magnitude of the echoes produced by the acoustic waves is measured, as is the time delay between the excitation pulses and the echoes from the liquid-material and material-substrate interfaces. The library and the acoustic wave detector are moved relative to one another in a raster scanning pattern and the collected data is recorded. Based upon the collected data an acoustic image of the library can be generated. The time-resolved image can give valuable information about library topography. For example, the first echo provides information related to the impedance mismatching on the element-coupling liquid interface and the second echo provides information about the sound velocity distribution in the element material.~~

~~In a fourth embodiment of the invention, individual piezoelectric transducers are integrated into the substrate. Typically the transducers are fabricated into the substrate~~

~~using standard fabrication techniques. The library elements are then deposited onto the substrate such that each individual library element corresponds to an individual piezoelectric transducer. The transducers serve the dual function of exciting the acoustic wave and receiving the return wave.~~

~~FIG. 1 is an illustration of a transducer-lens system coupled to a library. The library is comprised of an array of elements 101 contained within or on a substrate 103. Substrate 103 is coupled to a tank 105 containing a coupling medium 107. Coupling medium 107, selected on the basis of its acoustic properties, is selected from a variety of liquids, for example, water, mercury, etc. A transducer-lens system 109 provides the acoustic waves that pass through liquid 107 and are coupled into elements 101 and substrate 103. Transducer-lens system 109 is also used to measure the magnitude and time delay between the excitation pulses and the echoes. If desired, the excitation transducer may be separate from the receiving transducer. As described above, transducer-lens 109 is scanned across the array in order to obtain information about the entire array. Alternatively, an array of transducer-lenses may be used (not shown) as is used in conventional ultrasound imaging.~~

~~FIG. 2 illustrates a combinatorial library synthesized on a substrate consisting of integrated piezoelectric transducers. In the preferred embodiment, the individual piezoelectric transducers 201 comprising the transducer array are directly incorporated into substrate 103. Each transducer 201 is aligned such that it is directly adjacent to a corresponding library element 101. Transducers 201 serve as both the transmitters and receivers of the acoustic energy. The output signals from transducers 201 can be multiplexed for serial readout. In an alternative embodiment, transducers 201 are mounted onto a separate substrate (not shown) that is brought into contact with substrate 103. In another alternative embodiment, substrate 103 is formed of a piezoelectric material and electrodes are attached directly under each library element (not shown).~~

~~Mechanical Oscillator Probes~~

~~Although ultrasonic transducers can be used to determine a variety of material properties, this technique is not suitable for all liquids. Typically the size of the~~

~~transducer and the cell should be much greater than the acoustic wavelength; otherwise the diffraction effects and steady waves within the cell become too complicated. For a cell on the order of a few centimeters, the frequency should be above 1 MHz. However complex liquids and solutions, such as polymer solutions, often behave like elastic gels at high frequencies due to their relaxation time corresponding to significantly lower frequencies.~~

~~The method and apparatus of the present invention focuses on using a mechanical resonator to generate and receive oscillations in a fluid composition for testing its characteristics in a combinatorial chemistry process or other process requiring analysis of the fluid composition's physical and/or chemical properties. Although the detailed description focuses on combinatorial chemistry and the measurement of a liquid composition's characteristics, the invention can be used in any application requiring measurement of characteristics of a fluid composition, whether the fluid is in liquid or vapor form. The fluid composition itself can be any type of fluid, such as a solution, a liquid containing suspended particulates, or, in some embodiments, even a vapor containing a particular chemical or a mixture of chemicals. It can also include a liquid composition undergoing a physical and/or chemical change (e.g. an increase in viscosity).~~

~~Shear-mode transducers as well as various surface-wave transducers can be used to avoid some of the problems associated with typical ultrasonic transducers. Since leaky surface acoustic waves decay exponentially with the distance from the sensor surface, such sensors tend to be insensitive to the geometry of the measurement volume, thus eliminating most diffraction and reflection problems. Furthermore, such sensors are cheap, reproducible, and can be used to construct high-throughput screening devices. Unfortunately the operation frequency of these sensors is also high, thus restricting their applicability as mentioned above. Moreover, at such frequencies only a very thin layer of liquid near the sensor surface will influence the response of the sensor. Thus modification of the surface of the sensor through adsorption of solution components will often result in dramatic changes in properties associated with the sensor.~~

~~To eliminate the effects of diffraction, acoustic wave interference, and measurement cell~~

~~geometry, it is preferable to use a transducer or sensor that does not excite acoustic waves. A sensor that is much smaller than the wavelength accomplishes these goals, providing an oscillator that ineffectively excites acoustic waves in the surrounding media. Designing the different parts of the sensor to oscillate in opposite phases can enhance this effect. In such a resonator most of the mechanical energy associated with the oscillation dissipates due to the viscosity, both shear and bulk, of the liquid involved in the oscillatory motion. The sensor produces a hydrodynamic flow velocity field that decays with the distance from sensor. Thus liquid at a distance a few times greater than the sensor dimension remains practically unperturbed. If the measurement cell is large enough to contain the field of perturbation, the device becomes insensitive to the cell geometry. Examples of suitable oscillators include piezoceramic and quartz resonators embodied in the form of a tuning fork, a unimorph, or a bimorph. FIGS. 3 and 4 illustrate the oscillation modes of tuning fork and bimorph/unimorph resonators, respectively.~~

~~Typically a system according to the invention uses an AC voltage source to excite oscillation of the resonator. The system also includes a receiver which measures the frequency response of the resonator in the liquid under test. The response of the resonator varies depending upon the viscosity, specific weight, and elasticity of the liquid under test. In some cases the dielectric constant and the conductivity of the liquid can influence the response of the resonator. If properties of the liquid vary with time, the response of the resonator will similarly vary. By calibrating the resonator to a set of standard liquids with known properties, the properties of an unknown liquid can be determined from the response of the resonator.~~

[0028] ~~Mechanical resonators, such as thickness shear mode (TSM) quartz resonators 10, are used in the present invention for measuring various physical properties of fluid compositions, such as a liquid's viscosity, molecular weight, specific weight, etc., in a combinatorial chemistry setting or other liquid measurement application. Referring to FIG.~~ The method and apparatus of the present invention focuses on using a mechanical resonator to generate and receive oscillations in a fluid composition for testing its characteristics in a combinatorial chemistry process or other process requiring analysis of the fluid composition's physical and/or chemical properties. Although the detailed description focuses on combinatorial chemistry and the measurement of a liquid composition's characteristics, the invention can be used in any application requiring measurement of characteristics of a fluid composition, whether the fluid is in liquid or vapor form. The fluid composition itself can be any type of fluid, such as a solution, a liquid containing suspended particulates, or, in some embodiments, even a vapor containing a particular chemical or a mixture of chemicals. It can also include a liquid composition undergoing a physical and/or chemical change (e.g. an increase in viscosity).

[0029] Mechanical resonators, such as thickness shear mode (TSM) quartz resonators 10, are used in the present invention for measuring various physical properties of fluid compositions, such as a liquid's viscosity, molecular weight, specific weight, etc., in a combinatorial chemistry setting or other liquid measurement application. Referring to FIG. 1a, TSM resonators 10 usually have a flat, plate-like structure where a quartz crystal 12 is sandwiched in between two electrodes 14. In combinatorial chemistry applications, the user first generates a "library", or large collection, of compounds in a liquid composition. Normally, each liquid composition is placed into its own sample well. A TSM resonator 10 connected to an input signal source (not shown) is placed into each liquid composition, and a variable frequency input signal is sent to each TSM resonator 10, causing the TSM resonator 10 to oscillate. The input signal frequency is swept over a predetermined range to generate a unique TSM resonator 10 response for each particular liquid. Because every compound has a different chemical structure and consequently different properties, the TSM resonator 10 response will be also be different for each compound. The TSM resonator response is then processed to generated a visual trace of the liquid composition being tested. An example of traces generated by the TSM resonator 10 for multiple liquid compositions is shown in FIG. 5a~~, TSM resonators 10 usually have a flat, plate-like structure where a quartz crystal 12 is sandwiched in between two electrodes 14. In combinatorial chemistry applications, the user first generates a "library", or large collection, of compounds in a liquid composition. Normally, each liquid composition is placed into its own sample well. A TSM resonator 10 connected to an input signal source (not shown) is placed into each liquid composition, and a variable frequency input signal is sent to each TSM resonator 10, causing the TSM resonator 10 to~~

~~oscillate. The input signal frequency is swept over a predetermined range to generate a unique TSM resonator 10 response for each particular liquid. Because every compound has a different chemical structure and consequently different properties, the TSM resonator 10 response will be also be different for each compound. The TSM resonator response is then processed to generate a visual trace of the liquid composition being tested. An example of traces generated by the TSM resonator 10 for multiple liquid compositions is shown in FIG. 12a.~~. Screening and analysis of each compound's properties can then be conducted by comparing the visual traces of each compound with a reference and/or with other compounds. In this type of application, the TSM resonator 10 serves both as the wave source and the receiver.

[0030] Two types of waves can be excited in liquids: compression waves (also called acoustic waves), which tend to radiate a large distance, on the order of hundreds of wavelengths, from the wave-generating source; and viscose shear waves, which decay almost completely only one wavelength away from the wave-generating source. In any liquid property testing, acoustic waves should be kept to a minimum because they will create false readings when received by the resonator due to their long decay characteristics. For typical prior art ultrasonic transducers/resonators, the resonator oscillation creates acoustic waves that radiate in all directions from the resonator, bounce off the sides of the sample well, and adversely affect the resonator response. As a result, the resonator response will not only reflect the properties of the liquid being measured, but also the effects of the acoustic waves reflecting from the walls of the sample well holding the liquid, thereby creating false readings. Using a sample well that is much greater than the acoustic wavelength does minimize the negative effects of acoustic waves somewhat, but supplying thousands of sample wells having such large dimensions tends to be impractical.

[0031] TSM resonators 10 primarily generate viscose shear waves and are therefore a good choice for liquid property measurement in combinatorial chemistry applications because they do not generate acoustic waves that could reflect off the sides of the sample wells and generate false readings. As a result, the sample wells used with the TSM resonators 10 can be kept relatively small, making it feasible to construct an array of sample wells for rapid, simultaneous testing of many liquids. The high stiffness of

TSM resonators 10, however, require~~s~~ them to be operated at relatively high frequencies, on the order of 8-10 MHz. This stiffness does not adversely affect measurement accuracy for many applications, though, making the TSM resonator an appropriate choice for measuring numerous liquid compositions.

[0032] However, TSM resonators 10 can be somewhat insensitive to the physical properties of certain liquids because the load provided by the surrounding liquid is less than the elasticity of the resonator. More particularly, the high operating frequencies of TSM resonators 10 make them a less desirable choice for measuring properties of certain liquid compositions, particularly high-molecular weight materials such as polymers. When high frequency waves are propagated through high molecular-weight liquids, the liquids tend to behave like gels because the rates at which such large molecules move correspond to frequencies that are less than that of the TSM resonator's oscillations. This causes the TSM resonator 10 to generate readings that sometimes do not reflect the properties at which the liquids will actually be used (most materials are used in applications where the low-frequency dynamic response is most relevant). Although it would be more desirable to operate the TSM resonator 10 at lower frequencies so that laboratory conditions reflect real world conditions, the stiffness of the TSM resonator 10 and its resulting high operating frequencies can make operation at lower frequencies rather difficult. Further, even when the TSM resonator 10 can accurately measure a liquid's properties, the differences in the visual traces associated with different compositions are relatively slight, making it difficult to differentiate between compositions having similar structures, as shown in FIG. ~~12a.~~5a.

[0033] TSM resonators and other plate-type resonators, while adequate, may not always be the best choice for measuring the electrical characteristics, such as the dielectric constant, of the liquid composition being measured. As shown in FIG. ~~5a~~1a, the cross-section of a TSM resonator 10 has the same structure as a flat capacitor, resulting in relatively little coupling between the electric field of the resonator and the surrounding composition. While there can be enough electrical coupling between the resonator and the composition to measure the composition's electrical properties, a greater amount of electrical coupling is more desirable for increased measurement accuracy. Electrical coupling will be explained in greater detail below when comparing the electrical characteristics between the TSM resonator 10 and the tuning fork resonator 20.

[0034] FIGS. ~~5a~~1a and ~~5b~~1b show a cross-section of a TSM resonator plate 10 and a tuning fork tine 22, respectively. The tuning fork resonator 20 is preferably made from a quartz crystal 24 and has two tines 22, as represented in FIG. ~~3~~2, each tine having the quartz crystal center 24 and at least one electrode 26 connected to the quartz crystal 24. The tuning fork tines 22 in the preferred structure have a square or rectangular cross-section such that the quartz crystal center 24 of each tine has four faces. The electrodes 26 are then attached to each face of the quartz crystal center 24, as shown in FIG. ~~5b.~~1b. The method and system of the present invention can use any type of tuning fork resonator, such as a trident (three-prong) tuning fork or tuning forks of different sizes, without departing from the spirit and scope of the invention.

[0035] The cross-sectional views of the TSM resonator 10 and the tuning fork resonator 20 shown in FIGS. ~~5a~~1a and ~~5b~~1b also illustrate the relative differences between the electric coupling of each resonator with the surrounding liquid. Referring to FIG. ~~5a~~1a, the structure of the TSM resonator 10 is very flat, making it close to a perfect capacitor when it is placed in the liquid to be measured. As noted above, the quartz crystal 12 in the TSM resonator 10 is sandwiched between two electrodes 14, causing most of an electric field 16 to travel between the two electrodes through the quartz crystal 12. Because most of the electric field 16 is concentrated within the quartz crystal 12 rather than outside of it, there is very little electric coupling between the TSM resonator 10 and the surrounding liquid except at the edges of the resonator 10. While there may be sufficient electrical coupling to measure the electrical properties, such as the conductivity or dielectric constant, of the liquid composition being tested, a greater degree of coupling is desirable to ensure more accurate measurement.

[0036] By comparison, as shown in FIG. ~~5b~~1b, the structure of each tuning fork tine 22 allows much greater electrical coupling between the tine 22 and the surrounding liquid because the tuning fork tine's cross-sectional structure has a much different structure than a flat capacitor. Because the tuning fork tine 22 is submerged within the liquid being tested, an electric field 27 associated with each tine 22 does not concentrate in between the electrodes 24 or within the quartz crystal 24, but instead interacts outside the tine 22 with the surrounding liquid. This increased electrical coupling allows the tuning fork 20 to measure accurately the electrical properties of the liquid as well as its physical properties, and it can measure both types of properties simultaneously if so desired.

[0037] One unexpected result of the tuning fork resonator 20 is its ability to suppress the generation of acoustic waves in a liquid being tested, ensuring that the resonator's 20 physical response will be based only on the liquid's physical properties and not on acoustic wave interference or the shape of the sample well holding the liquid. As explained above, TSM resonators 10 minimize excitation of acoustic waves because it generates shear oscillations, which do not excite waves normal to the resonator's surface. As also explained above, however, the TSM resonator 10 requires high frequency operation and is not suitable for many measurement applications, particularly those involving high-molecular weight liquids.

[0038] Without wishing to be bound by any particular theory, the inventors believe that the tuning fork resonator 20 used in the present invention virtually eliminates the effects of acoustic waves without having to increase the size of the sample wells to avoid wave reflection. Tuning fork resonators 20, because of their shape and their orientation in the liquid being tested, contain velocity components normal to the vibrating surface. Thus, it was assumed in the art that tuning fork resonators were unsuitable for measuring liquid properties because they would generate acoustic waves causing false readings. In reality, however, tuning fork resonators 20 are very effective in suppressing the generation of acoustic waves for several reasons. First, the preferred size of the tuning fork resonator 20 used in the invention is much smaller than the wavelength of the acoustic waves that are normally generated in a liquid, as much as one-tenth to one-hundredth the size. Second, as shown in FIG. 3, the tines 22 of the tuning fork resonator 20 oscillate in opposite directions, each tine 22 acting as a separate potential acoustic wave generator. In other words, the tines 22 either move toward each other or away from each other. Because the tines 22 oscillate in opposite directions and opposite phases, however, the waves that end up being generated locally by each tine 22 tend to cancel each other out, resulting in virtually no acoustic wave generation from the tuning fork resonator 22 as a whole.

[0039] A simplified diagram of one example of the inventive mechanical resonator 20 system is shown in FIG~~ 6.~~. 2. Although the explanation of the system focuses on using the tuning fork resonator 20, the TSM resonator 10 described above can also be used for the same purpose. To measure the property of a given liquid, the tuning fork resonator 20 is simply submerged in the liquid to be tested. A variable frequency input signal is then sent to the tuning fork resonator using any known means to oscillate the tuning fork, and the input signal frequency is swept over a predetermined range. The tuning fork resonator's response is monitored and recorded. In the example shown in FIG. ~~6~~2, the tuning fork resonator 20 is placed inside a well 26 containing a liquid to be tested. This liquid can be one of many liquids for comparison and screening or it can simply be one liquid whose properties are to be analyzed independently. Further, if there are multiple liquids to be tested, they can be placed in an array and measured simultaneously with a plurality of tuning fork resonators to test many liquids in a given amount of time. The liquid can also be a liquid that is undergoing a polymerization reaction or a liquid flowing through a conduit.

[0040] The tuning fork resonator 20 is preferably coupled with a network analyzer 28, such as a Hewlett-Packard 8751A network analyzer, which sends a variable frequency input signal to the tuning fork resonator 20 to generate the resonator oscillations and to receive the resonator response at different frequencies. The resonator output then passes through a high impedance buffer 30 before being measured by a wide band receiver 32. The invention is not limited to this specific type of network analyzer, however; any other analyzer that generates and monitors the resonator's response over a selected frequency range can be used without departing from the scope of the invention. For example, a sweep generator and AC voltmeter can be used in place of the network analyzer.

~~In one embodiment of the invention illustrated in~~An equivalent circuit of the tuning fork resonator 20 and its associated measurement circuit is represented in FIGS. 4a and 4b. FIG. ~~6, a tuning fork resonator system 500 is used to monitor the average molecular weight of polystyrene in toluene solutions during polymerization reactions. This configuration is not limited to this polymerization reaction; rather, the polymerization reaction is simply used as an example of an application of this embodiment. The~~

~~monitoring of the forming polymer's properties in the presence of a polymerization catalyst and possibly a solvent is essential in order to estimate catalytic activity and conversion rate.~~

~~In use, a tuning fork resonator 501 is placed within a well 503 containing the liquid to be tested. Preferably well 503 is one well of a plurality of wells contained within an array. Resonator 501 is typically coupled to a probe and the probe is scanned from sample well to sample well in a raster fashion. Alternatively, an array of resonator probes can be fabricated corresponding to the array of wells or some subset thereof, thus allowing a large number of wells to be simultaneously tested. In the embodiment illustrated in FIG. 6, a network analyzer 505, such as a HP8751A Analyzer, is used to excite the resonator oscillations and to receive the response of the oscillator at various frequencies. Resonator response is then recorded as a function of excitation frequency. The output signal of resonator 501 passes through a high impedance buffer amplifier 507 prior to being measured by the analyzer's wide band receiver 509.~~

~~System 500 was calibrated using a set of standard solutions of polystyrene at a constant concentration of 52 mg/ml. In pure toluene, the frequency of the resonator fundamental mode was 28 kHz. FIG. 7 is a graph of the frequency responses of resonator 501 for pure toluene and four different molecular weights of polystyrene. The distance between the frequency response curve for toluene and an i-polymer solution was calibrated using the set of different molecular weights. This distance is given by:~~

$$d_i = \left(\frac{1}{f_1 - f_0} \int_{f_0}^{f_1} \left(R_0 - R_i\right)^2 df \right)^{\frac{1}{2}}$$

~~where f_0 and f_1 are the start and stop frequencies, respectively, R_0 is the frequency response of the resonator in toluene, and R_i is the resonator response in the i-polymer solution.~~

~~FIG. 8 is a graph of a calibration curve corresponding to this data. The test points and associated error bars are indicated on this curve. Obviously additional calibration curves can be taken as necessary. The graph of FIG. 8 shows that for this particular resonator design, the best accuracy is achieved for molecular weights in the range of 10,000 to~~

~~100,000.~~

~~To monitor a polymerization reaction, resonator probe 501 is placed in a measurement well 503 filled with pure toluene and the catalyst. The frequency response of the sensor for this solution is recorded. Resonator probe 501 is then placed in a measurement well 503 filled with toluene in which a low molecular weight polystyrene has been dissolved. After the catalyst is added, the frequency response of the resonator is recorded at intervals, typically between 10 and 30 seconds. The distance of the response curve for the polymer from that of pure toluene is then calculated in accordance with the formula given above. The molecular weight of the polymer is calculated using the calibration curve of FIG. 8.~~

~~As discussed above, depending upon the liquid to be tested, other resonator designs may be used. For example, to improve the suppression of acoustic waves, a tuning fork resonator with four tines can be used. It is also possible to excite resonator oscillations through the use of voltage spikes instead of a frequency sweeping AC source. In this case the decaying free oscillations of the resonator are recorded instead of the frequency response. A variety of signal processing techniques well known by those of skill in the art can be used.~~

[0041] ~~An equivalent circuit of the tuning fork resonator 20 and its associated measurement circuit is represented in FIGS. 9a and 9b. FIG. 9a~~4a represents an illustrative tuning fork resonator system that measures a liquid's viscosity and dielectric constant simultaneously, while FIG. ~~9b~~4b represents a tuning fork resonator system that can also measure a liquid's conductivity as well. Referring to FIG. ~~9a~~4a, the measurement circuit includes a variable frequency input signal source 42, and the resonator equivalent circuit 43 contains series capacitor Cs, resistor Rs, inductor L, and parallel capacitor Cp. The resonator equivalent circuit 43 explicitly illustrates the fact that the quartz crystal 24 in the tuning fork resonator 20 acts like a capacitor Cp. The representative circuit 40 also includes input capacitor Cin, input resistor Rin and an output buffer 44.

[0042] The representative circuit shown in FIG. ~~9b~~4b adds a parallel resistor Rp in parallel to capacitor Cp to illustrate a circuit that measures conductivity as well as dielectric constant and viscosity, preferably by comparing the equivalent resistance found in a given liquid with a known resistance found via calibration. These concepts will be explained in further detail below with respect to FIGS. ~~12a~~5a-b, ~~13a~~6a-b, ~~14a~~7a-b, and ~~15a~~8a-b. Rp represents the conductivity of the liquid being tested. The resistance can be calibrated using a set of liquids having known conductivity and then used to measure the conductivity of a given liquid. For example, FIG. 4c shows a sample trace comparing the resonator response in pure toluene and in KaBr toluene solution. A liquid having greater conductivity tends to shift the resonator response upward on the graph, similar to liquids having higher dielectric constants. However, unlike liquids with higher dielectric constants, a liquid having greater conductivity will also cause the resonator response to level out somewhat in the frequency sweep, as can be seen in the upper trace 45 between 30 and 31.5 kHz. In the example shown in FIG. ~~9c~~4c, the difference between the upper trace 45 and the lower trace 46 indicates that the equivalent resistance Rp caused by the additional KaBr in solution was about 8 mega-ohms.

~~FIG. 10 illustrates an embodiment of the invention that can be used for high throughput screening of catalyst combinatorial libraries. The embodiment monitors the molecular weight and concentration, if necessary, of a polymer in a solution in the presence of different catalysts while the reactions are running. Preferably the system also includes means for monitoring the heat generated during the reactions. Thus hundreds of catalysts can be evaluated in a single experiment for such characteristics as selectivity, conversion rate, etc.~~

~~An array of measurement wells 801 is contained within a substrate 803. Within each well 801 is a resonator 805 for molecular weight determination and a thermistor 807 for heat of reaction determination. Preferably contacts 809 for resonator 805 and thermistor 807 pass through the bottom of substrate 803 where they are connected to the necessary electronics. Much of the electronics can be mounted directly to the bottom of substrate 803, simplifying the overall system design. However, as previously described, the array of resonator probes can also be fabricated as a stand alone array to be placed within the corresponding measurement wells of a combinatorial library array during testing.~~

~~The measurement package within each well 801 may also contain an agitator 811 to~~

~~insure uniform concentration distribution within the well. Typically agitator 811 is not required if well 801 is small enough to promote rapid concentration leveling due to diffusion. Besides monitoring the heat generated during the reactions, thermistors 807 may also be used to preheat the media within wells 801 up to a predefined temperature and to keep the temperature at the same level during the reactions. In a specific embodiment, a thermostatically controlled cooling liquid 813 passes between the walls of wells 801, thus providing a steady heat transfer from wells 801.~~

~~FIG. 11 is a simplified circuit diagram for a multiplexed control circuit suitable for use with the embodiment shown in FIG. 10. Although only three measurement cells 901 are shown, this control circuit can be used to multiplex a large array of cells. The output of a resonator 903 passes through a local buffer amplifier 905 before being multiplexed into a data acquisition system 907. Coupled to each thermistor 909 is a thermostat 911. The heat produced by a reaction causes local thermostat 911 to drop down the voltage across thermistor 909 to keep its temperature at the same level. As with the resonator output, this voltage is multiplexed and acquired by data acquisition system 907. Thus the heat production given by each reaction can be easily calculated at any time, providing information about the activity of a particular catalyst. The data acquired by system 907 is processed by processor 913 and presented to the user via monitor 915. The data may also be stored in memory resident within processor 913. From this data the reactions occurring in the various wells may be simultaneously characterized.~~

[0043] ~~In an alternate embodiment, multiple resonators are used within each single well of an array. The multiple resonators typically have a different resonance frequency and/or geometry. This embodiment offers several advantages to the previous embodiment utilizing a single resonator per well. First, the dynamic sensing range of the system may be greatly extended since each of the individual resonators may be designed to cover a different frequency range. Second, the sensitivity over the sensing range may be enhanced since each resonator may be designed to be sensitive to a different frequency range. For example, the graph illustrated in FIG. 8 shows that for this particular resonator design, the best accuracy was achieved for molecular weights in the range of 10,000 to 100,000. Utilizing the present embodiment, a resonator with the accuracy shown above could be combined in a single sample well with a resonator~~

~~having improved accuracy in the 100,000 to 1,000,000 range, thus providing superlative sensing capabilities throughout the 10,000 to 1,000,000 range for a single sample well. The signals from the independent resonators may be analyzed using such methods as neural networks, etc.~~Experimental Examples

[0044] FIGS. ~~12a~~5a-b, ~~13a~~6a-b, ~~14a~~7a-b and ~~15a~~8a-b are examples demonstrating the effectiveness of the invention. These figures show some differences between the frequency responses, for various liquid compositions, of the plate-type TSM resonator 10 and the tuning fork resonator 20. FIGS. ~~12a, 13a, 14a and 15a~~5a, 6a, 7a and 8a are examples using the TSM resonator 10, and FIGS. ~~12b, 13b, 14b and 15b~~5b, 6b, 7b and 8b are examples using the tuning fork resonator 20.

[0045] The experimental conditions for generating the example tuning fork resonator traces in FIGS. ~~12b, 13b, 14b, and 15b~~5b, 6b, 7b, and 8b are described below. The experimental conditions for generating the comparative TSM resonator traces in FIGS. ~~12a, 13a, 14a and 15a~~5a, 6a, 7a and 8a are generally similar to, if not the same as, the conditions for the tuning fork resonator except for, if needed, minor modifications to accommodate the TSM resonator's particular geometry. Therefore, for simplicity and clarity, the TSM resonator's particular experimental conditions will not be described separately.

[0046] All of the solvents, polymers and other chemicals used in the illustrated examples were purchased from Aldrich, and the polymer solutions were made according to standard laboratory techniques. Dry polymers and their corresponding solvents were weighed using standard balances, and the polymer and solvent were mixed until the polymer dissolved completely, creating a solution having a known concentration. The solutions were delivered to and removed from a 30 ul stainless steel cylindrical measurement well that is long enough to allow a tuning fork resonator to be covered by liquid. Liquid delivery and removal to and from the well was conducted via a pipette or syringe.

[0047] Before any experiments were conducted with the solutions, the tuning fork resonator response in air was measured as a reference. The actual testing processes were conducted in a temperature-controlled laboratory set at around 20 degrees Centigrade. Once the liquid was delivered to the well, the tuning fork was placed in the well and the system was left alone to allow the temperature to stabilize. Alternatively, the tuning fork can be built into a wall portion or a bottom portion of the well with equally accurate results. The tuning fork was then oscillated using the network analyzer. The resonator response was recorded during each measurement and stored in a computer memory. The measured response curve was fitted to a model curve using an equivalent circuit, which provided specific values for the equivalent circuit components described above with respect to FIGS. ~~9a~~4a and ~~9b~~4b and the traces in FIGS. ~~13a~~6a through ~~15b~~8b.

[0048] After the measurement of a given solution was completed, the resonator was kept in the well and pure solvent was poured inside the well to dissolve any polymer residue or coating in the well and on the tuning fork. The well and tuning fork were blown dry using dry air, and the tuning fork response in air was measured again and compared with the initial tuning fork measurement to ensure that the tuning fork was completely clean; a clean tuning fork would give the same response as the initial tuning fork response. Note that the above-described experimental conditions are described only for purposes of illustration and not limitation, and those of ordinary skill in the art would understand that other experimental conditions can be used without departing from the scope of the invention.

[0049] Although both the TSM resonator 10 and the tuning fork resonator 20 are considered to be part of the method and system of the present invention, the tuning fork resonator 20 has wider application than the TSM resonator 10 and is considered by the inventors to be the preferred embodiment for most measurement applications because of its sensitivity, availability and relatively low cost. For example, note that in FIGS. 5a and 5b, the frequency sweep for the TSM resonator 10 is in the 8MHz range, while the frequency sweep for the tuning fork resonator 20 of the present invention is in the 25-30 kHz range, several orders of magnitude less than the TSM resonator frequency sweep range. This increases the versatility and applicability of the tuning fork resonator 20 for measuring high molecular weight liquids because the operating frequency of the tuning fork resonator 20 is not high enough to make high molecular weight liquids act like gels. Further, because most applications for the solutions are lower frequency applications, the laboratory conditions in which the liquid compositions are tested using the tuning fork resonator 20 more closely correspond with real-world conditions.

[0050] Also, the operating frequency of the tuning fork resonator 20 varies according to the resonator's geometry; more particularly, the resonance frequency of the tuning fork 20 depends on the ratio between the tine cross-sectional area and the tine's length. Theoretically, it is possible to construct a tuning fork resonator 20 of any length for a given frequency by changing the tuning fork's cross-sectional area to keep the ratio between the length and the cross-section constant. In practice, however, tuning fork resonators 20 are manufactured from quartz wafers having a few selected standard thicknesses. Therefore, the cross-sectional area of the tuning fork 20 tends to be limited based on the standard quartz wafer thicknesses, forcing the manufacturer to change the tuning fork's resonating frequency by changing the tine length. These manufacturing limitations must be taken into account when selecting a tuning fork resonator 20 that is small enough to fit in minimal-volume sample wells (because the chemicals used are quite expensive) and yet operates at a frequency low enough to prevent the tested liquids from acting like gels. Of course, in other applications, such as measurement of liquids in a conduit or in other containers, the overall size of the tuning fork resonator 20 is not as crucial, allowing greater flexibility in selecting the size and dimensions of the tuning fork resonator 20. Selecting the actual tuning fork dimensions and designing a tuning fork resonator in view of manufacturing limitations are tasks that can be conducted by those of skill in the art after reviewing this specification.

[0051] Referring to FIGS. ~~12a~~5a and ~~12b~~5b, the solutions used as examples in FIGS. ~~12a~~5a and ~~12b~~5b have somewhat similar structures and weights. As a result, the TSM resonator responses for each solution, shown in FIG. ~~12a~~5a, create very similar traces in the same general range. Because the traces associated with the TSM resonator 10 overlap each other to such a great extent, it is difficult to isolate and compare the differences between the responses associated with each solution. By comparison, as shown in FIG. ~~17b~~5b, the increased sensitivity of the tuning fork resonator 20 causes small differences in the chemical structure to translate into significant differences in the resonator response. Because the traces generated by the tuning fork resonator 20 are so distinct and spaced apart, they are much easier to analyze and compare.

[0052] Using a tuning fork resonator 20 to measure properties of liquids also results in greater linearity in the relationship between the square root of the product of the liquid's viscosity density and the equivalent serial resistance Rs (FIGS. ~~13a~~6a and ~~13b~~6b) as well as in the relationship between the dielectric constant and the equivalent parallel capacitance Cp (FIGS. ~~14a~~7a and ~~14b~~7b) compared to TSM resonators 10. For example, the relationship between the liquid viscosity and serial resistance for a tuning fork resonator 20, as shown in FIG. ~~13b~~6b, is much more linear than that for the TSM resonator, as shown in FIG. ~~13a.~~6a.

[0053] Similarly, the relationship between the dielectric constant and the equivalent parallel capacitance is more linear for a tuning fork resonator 20, as shown in FIGS. ~~14a~~7a and ~~14b.~~7b. This improved linear relationship is primarily due to the relatively low frequencies at which the tuning fork resonator 20 operates; because many liquids exhibit different behavior at the operating frequencies required by the TSM resonator 10, the TSM resonator 10 will tend not to generate testing results that agree with known data about the liquids' characteristics.

[0054] FIGS. ~~15a~~8a and ~~15b~~8b illustrate sample results from real-time monitoring of polymerization reactions by a TSM resonator and a tuning fork resonator, respectively. The graphs plot the equivalent resistance Rs of the resonators oscillating in 10 and 20 mg/ml polystyrene-toluene solutions versus the average molecular weight of polystyrene. As explained above, high molecular weight solutions often exhibit different physical characteristics, such as viscosity, at higher frequencies.

[0055] The size and shape of the TSM resonator 10 make the resonator suitable, but not as accurate, for real-time monitoring of polymerization reactions compared with the tuning fork resonator 20. This is because the TSM resonator's high operating frequency reduces the accuracy of measurements taken when the molecular weight of the polymerizing solution increases. As shown in FIG. ~~15a~~8a, a high operating frequency TSM resonator is not very sensitive in monitoring the molecular weight of the polystyrene solution used in the illustrated example. A tuning fork resonator, by contrast, has greater sensitivity to the molecular weight of the solution being measured, as shown in FIG. ~~15b.~~8b. This sensitivity and accuracy makes it possible, for many reactions, to estimate the amount of converted solution in the polymerization reaction and use the conversion data to estimate the average molecular weight of the polymer being produced.

[0056] Although the above-described examples describe using a TSM or a tuning fork resonator without any modifications, the resonator can also be treated with a "functionality" (a specialized coating) so that it is more sensitive to certain chemicals. The resonator may also be treated with a general coating to protect the resonator from corrosion or other problems that could impede its performance. A representative diagram of an embodiment having a functionalized resonator is shown in FIGS. ~~16a~~9a and ~~16b.~~9b. Although FIGS. ~~16a~~9a and ~~16b~~9b as well as the following description focuses on coating or functionalizing a tuning fork resonator, any other mechanical resonator can also be used without departing from the scope of the invention.

[0057] The tuning fork resonator 20 can be coated with a selected material to change how the resonator 20 is affected by a fluid composition (which, as explained earlier, includes both liquid and vapor compositions). As mentioned above, one option is a general coating for providing the tuning fork resonator 20 with additional properties such as corrosion resistance, chemical resistance, electrical resistance, and the like. Another option, as noted above, is using a "functionality", which coats the tines with materials that are designed for a specific application, such as proteins to allow the tuning fork resonator 20 to be used as a pH meter or receptors that attract specific substances in the fluid composition to detect the presence of those substances. The coating or functionality can be applied onto the tuning fork resonator 20 using any known method, such as spraying or dipping. Further, the specific material selected for the coating or functionality will depend on the specific application in which the tuning fork resonator 20 is to be used. J. Hlavay and G. G. Guilbault described various coating and functionalization methods and materials to adapt piezoelectric crystal detectors for specific applications in "Applications of the Piezoelectric Crystal Detector in Analytical Chemistry," Analytical Chemistry, Vol. 49, No. 13, November 1977, p. 1890, incorporated herein by reference. For example, applying different inorganic functionalities to the tuning fork resonator 20 allows the resonator to detect organophosphorous compounds and pesticides.

[0058] An example of a tuning fork resonator that has undergone a functionalization treatment is illustrated in FIGS. ~~16a~~9a and ~~16b.~~9b. FIG. ~~16a~~9a represents a tuning fork tine 22 that has been treated by absorbing, coating, or otherwise surrounding the tine 22 with a functionality designed to change the tuning fork's resonance frequency after being exposed to a selected target chemical. In the illustrated example, the tuning fork tine 22 is covered with receptor molecules 90, represented in FIGS. ~~16a~~9a and ~~16b~~9b by Y-shaped members, designed to bond with specific target molecules. Because the resonance frequency and the damping of the tuning fork resonator depends on the effective mass of the tine 22 and the amount of "drag" of the tine 22 within the fluid, any change in the tine's mass or the amount of drag will change the tuning fork's resonance response. More specifically, the resonance frequency of the tuning fork resonator is proportional to the square root of the inverse of the tuning fork's mass. An increase in the tuning fork's mass will therefore reduce the tuning fork's resonance frequency.

[0059] This mass-frequency relationship is used to detect the presence of a specific target chemical in a fluid composition in this example. When the functionalized tuning fork tine 22 is placed in a fluid composition containing the target chemical, the receptors 90 on the tuning fork tine 22 will chemically bond with molecules of the target chemical 92, as shown in FIG. ~~16b.~~9b. The resonance frequency of the tuning fork resonator will consequently decrease because of the increased mass and the additional drag created by the additional molecules 92 attached to the tuning fork tines 22 via the receptor molecules 90. Thus, when screening a plurality of fluid compositions to detect the presence of a target chemical in any of them, only the fluid compositions containing the target chemical will cause the tuning fork's resonance frequency to change. Fluid compositions without the target chemical will not contain molecules that will bond with the receptor molecules 90 on the tuning fork tine 22, resulting in no resonance frequency change for those fluids. Alternatively, the tuning fork tines 22 can be functionalized with a material that physically changes when exposed to molecules of a selected chemical such that the material changes the mechanical drag on the tuning fork tine 22 when it is exposed to the selected chemical. For example, adding a hydrophobic or hydrophilic functionality to the tuning fork tine 22 allows the tine 22 to attract or repel selected substances in the medium being analyzed, changing the mass or effective mass of the tuning fork and thereby changing its resonance frequency.

[0060] In yet another embodiment of the present invention, multiple mechanical resonators can be attached together in a single sensor to measure a wider range of responses for a given fluid composition, as shown in FIGS. ~~17a, 17b and 17c.~~10a, 10b and 10c. The multiple resonator sensor can be fabricated from a single quartz piece such that all of the resonators are attached together by a common base, as shown in the figures. The multi-resonator sensor could also be attached to multiple frequency generating circuits, such as multiple network analyzers 28, to measure properties of the fluid compositions over multiple frequency sweeps so that the generated data can be correlated to obtain additional information about the liquid compositions. Because different resonator structures are best suited for measurement over different frequency ranges and for materials having different characteristics, a sensor combining a plurality of different resonators can provide a more complete representation of the fluid composition's characteristics over a wider frequency range than a single resonator. FIGS. ~~17a, 17b~~10a, 10b and ~~17c~~10c show specific examples of possible multi-resonator configurations, but those of skill in the art would understand that sensors having any combination of resonators can be constructed without departing from the scope of the invention.

[0061] FIG. ~~17a~~10a illustrates one possible sensor 100 configuration containing both a tuning fork resonator 102 and a TSM resonator 104. This type of sensor 100 can be used to, for example, measure the mechanical and electrical properties of very thick liquids such as polymer resins and epoxies. This sensor 100 can also be used to monitor a material as it polymerizes and hardens. For example, the sensor 100 can be placed in a liquid composition containing urethane rubber in its diluted state so that the tuning fork 102 is used initially to measure both the composition's density viscosity product and its dielectric constant. As the rubber changes to a gel and finally to a solid, the sensor 100 can switch to using the TSM resonator 104 to measure the rubber's mechanical properties, leaving the tuning fork resonator 102 to operate as a dielectric sensor only.

[0062] A sensor 106 for observing a fluid composition over a wide frequency range is shown in FIG. 10b. High polydispersity polymer solutions are ideally measured over a wide frequency spectrum, but most resonators have optimum performance within a relatively limited frequency range. By combining different resonators having different resonance frequencies and different response characteristics, it is possible to obtain a more complete spectrum of resonator responses for analyzing the fluid's characteristics under many different conditions. For example, due to the wide spectrum of polydisperse solution relaxation times, it is generally predicted that high molecular weight compositions will react at lower frequencies than lighter molecular weight compositions. By changing the temperature, observing the frequency response of different resonators, and correlating the different resonator responses, it is possible to obtain a more accurate picture of a composition's relaxation spectrum than from a single resonator.

[0063] A low frequency tuning fork resonator 108 and a high frequency tuning fork resonator 110 in one sensor will probably suffice for most wide-frequency range measurements. For certain cases, however, the resonators in the multi-resonator sensor 106 can also include a trident tuning fork resonator 112, a length extension resonator 114, a torsion resonator 116, and a TSM resonator 118, membrane oscillators, bimorphs, unimorphs, and various surface acoustic wave devices, as well as any combination thereof, or even a single resonator structure than can operate in multiple mechanical modes (e.g. compression mode, axial mode, torsion mode). Of course, not all of these resonators are needed for every application, but those of skill in the art can select different combinations that are applicable to the specific application in which the sensor 106 will be used.

[0064] Alternatively, multiple resonators having the same structure but different coatings and/or functionalities can be incorporated into one sensor 120, as shown in FIG. ~~17c.~~ 10c. In this example, a plurality of tuning fork resonators 122, 124, 126 have the same structure but have different functionalities, each functionality designed to, for example, bond with a different target molecule. The high sensitivity of the tuning fork resonators 122, 124, 126 makes them particularly suitable for "artificial noses" that can detect the presence of an environmentally-offending molecule, such as hydrogen sulfide or nitrous oxide, in industrial emissions. When the sensor 120 is used in such an application, one tuning fork resonator 122 can, for example, be functionalized with a material designed to bond with hydrogen sulfide while another resonator 124 can be functionalized with a material designed to bond with nitrous oxide. The presence of either one of these molecules in the fluid composition being tested will cause the corresponding tuning fork resonator 122, 124 to change its resonance frequency, as explained with respect to FIGS. ~~16a~~9a and ~~16b~~9b.

[0065] The tuning fork resonators 122, 124, 126 can also be functionalized with a polymer layer or other selective absorbing layer to detect the presence of specific molecules in a vapor. Because the tuning fork resonators 122, 124, 126 are highly sensitive to the dielectric constant of the surrounding fluid, the tuning fork resonators 122, 124, 126 can easily detect changes in the dielectric constant of the fluid and recognize a set of solvents with different dielectric constants in the fluid. This information, combined with other observable parameters, makes tuning fork resonators particularly adaptable for use in artificial noses.

[0066] The method and system of the present invention has been described above in the combinatorial chemistry context, but it is not limited to such an application. Because the resonators in the method and system of the present invention have high sensitivities and quick response times, it can be also be used for in-line monitoring of fluid compositions flowing through conduits or pipelines. For example, the invention can be used in a feedback system to monitor properties of liquids flowing through a gas or oil pipeline to monitor and control the concentration of additives in the gas or oil, or to detect the presence of impurities in water flowing through a water pipe. The additives or impurities will change the physical and electrical characteristics of the liquid flowing through the conduit. A functionalized tuning fork resonator 20 can further detect the presence of a specific chemical in a fluid composition, whether it is a liquid or a vapor, and can be used to monitor the presence of, for example, a known chemical pollutant in a smokestack. The high sensitivity and quick response time of the resonator, and the tuning fork resonator 20 in particular, makes it uniquely suitable for such an application. The circuitry and system used to generate the visual traces from the resonator's response can be the same as described above or be any other equivalent resonator analysis system.

[0067] Further, although the above description focuses primarily on using TSM resonators and tuning fork resonators, any other mechanical resonators exhibiting similar characteristics can be used. Tridents, cantilevers, torsion bars, bimorphs, and/or membrane resonators can be substituted for the TSM resonator or tuning fork resonator without departing from the scope of the claimed invention.

[0068] It should be understood that various alternatives to the embodiments of the invention described herein may be employed in practicing the invention. It is intended that the following claims define the scope of the invention and that the methods and apparatus within the scope of these claims and their equivalents be covered thereby.

~~It is understood that the above description is intended to be illustrative and not restrictive. Many embodiments as well as many applications besides the examples provided will be apparent to those of skill in the art upon reading the above description. The scope of the invention should, therefore, be determined not with reference to the above description, but should instead be determined with reference to the appended claims, along with the full scope of equivalents to which such claims are entitled. The disclosures of all articles and references, including patent applications and publications, are incorporated by reference for all purposes.~~